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Review article

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Expanding global access to mRNA vaccines

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Abstract

mRNA vaccines benefit from rapid design, scalable manufacturing and strong safety profiles, and they are being preclinically and clinically explored for various infectious diseases, cancer and autoimmune disorders. However, global access to mRNA vaccines remains limited by technical, logistical, economic, regulatory and ethical challenges. In this Review, we discuss the current mRNA vaccine landscape, from approved products to emerging candidates, and outline key barriers to equitable access. We highlight engineering strategies to address these barriers, including thermostability improvements, alternative administration routes, new delivery systems and alternative RNA platforms, such as self-amplifying and circular RNA, as well as the integration of artificial intelligence- and machine learning-based design and optimization. We also discuss the regulatory, ethical and social dimensions of vaccine deployment, as well as the importance of building public trust and community engagement. Coordinated technical and policy advances are essential to remove barriers, enhance access and advance global health equity.

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Key points

- The success of COVID-19 mRNA vaccines established a robust platform that is now expanding to other infectious diseases and non-infectious diseases, including cancer and autoimmune disorders.
- The full potential of mRNA vaccines can only be realized through broad accessibility.
- Expanding mRNA vaccine access requires integrated engineering strategies, including thermostability improvements, alternative delivery routes, new carriers and RNA platforms, such as self-amplifying and circular constructs.
- Artificial intelligence-driven and machine learning-driven mRNA vaccine design and optimization could shorten iteration times, accelerate progress from development to scalable manufacturing and support expanded access.
- Equitable mRNA vaccine access requires coordinated policy, regulatory and community actions that harmonize global regulations, secure sustained global funding, and engagement of communities to address vaccine hesitancy.

Introduction

The success of mRNA vaccines during the COVID-19 pandemic demonstrated their speed of development, scalable manufacturing, adaptability to viral variants and strong safety profile[1–5]. These advantages have established mRNA platforms as a cornerstone of next-generation vaccines and therapeutics[1,6–9]. Central to this success are lipid nanoparticles (LNPs), which protect mRNA from degradation and enable efficient intracellular delivery[10]. Most mRNA–LNPs comprise four components: an ionizable lipid (for mRNA complexation and endosomal escape), cholesterol (to enhance membrane packing and stability), a helper phospholipid (to modulate fluidity and promote endosomal fusion) and a polyethylene glycol (PEG)-lipid (to control particle size, provide steric stabilization and prolong circulation)[1,10]. The platform underlying mRNA vaccines has been in development over several decades; mRNA was identified in 1961, and initial first-in-human clinical trials of mRNA-based therapeutics date to the early 2000s[6,7].

Leveraging their ability to encode diverse antigens with precision, mRNA vaccines are now being developed for various infectious diseases, including influenza, human immunodeficiency virus (HIV), Zika virus, tuberculosis and malaria[1,11,12], as well as non-infectious diseases, including cancer[13,14] and autoimmune disorders[15]. However, realizing their global impact requires addressing persistent accessibility challenges, particularly in settings with limited resources, in which cold-chain dependence and complex manufacturing constrain distribution[16,17]. Although COVID-19 vaccination has saved millions of lives globally, the global death toll could have been further reduced with greater distribution and access[18]. The disproportionate availability of mRNA vaccines across different regions highlights the need for innovative strategies to enhance accessibility[18]. Ensuring that mRNA vaccines reach underserved populations is crucial for global health equity and pandemic preparedness[19]. The Coalition for Epidemic Preparedness Innovations (CEPI)-led 100 Days Mission outlines a global strategy to deliver diagnostics, therapeutics and vaccines within ~100 days of a new pandemic threat[20]. This strategy is built on multisector partnerships, regulatory harmonization, regionally distributed manufacturing, and a global network of clinical trials, as well as thermostable, context-appropriate products, and it is underpinned by pre-agreed guidelines on intellectual property, access to pathogen and clinical samples, surge financing, and product-liability sharing.

In this Review, we examine the expanding landscape of mRNA vaccines and therapeutics, and analyse key barriers to accessibility, including technical, logistical, economic and regulatory challenges. We highlight engineering strategies to improve stability, simplify administration and reduce dose requirements, including thermostability-enhancing formulations, alternative delivery routes, as well as new carriers and RNA platforms, such as self-amplifying and circular RNAs. We also discuss artificial intelligence (AI)-driven mRNA design and optimization, which have the potential to accelerate development and broaden access. Finally, we address ethical and social considerations essential for equitable deployment, including vaccine hesitancy and community engagement. Achieving the full potential of mRNA vaccines will require coordinated global efforts integrating public–private partnerships, regional manufacturing and regulatory alignment to ensure equitable and sustainable global access.

mRNA vaccines and therapeutics

The versatility of mRNA technology has catalysed a shift in vaccinology[6] owing to its capacity for rapid antigen design, scalable manufacturing and potent immunogenicity. Therefore, mRNA platforms are now being explored for a range of applications, including infectious diseases[21], oncology, rare genetic disorders and chronic infections[22], with several formulations approved or in clinical development[23] (Table 1). Most approved mRNA vaccines target SARS-CoV-2 and rely on nucleoside-modified mRNA platforms that require cold-chain storage, which limits their accessibility. By contrast, the COVID-19 vaccine mNEXSPIKE (mRNA-1283), which recently received US Food and Drug Administration (FDA) approval for use in adults 65 years of age and older, as well as individuals 12–64 years of age with at least one underlying condition associated with increased risk of severe COVID-19 (ref. 24), remains viable for up to 90 days at 2–8 °C and up to 24 hours at room temperature. This improved storage profile is a result of a thermostable optimized mRNA architecture; here, mRNA-1283 encodes linked N-terminal domain and receptor-binding domain segments, instead of the full-length spike protein. Similarly, the self-amplifying mRNA (saRNA) vaccines GEMCOVAC-19 and GEMCOVAC-OM are supplied as lyophilized powder and administered through needle-free injection, enabling storage and delivery without the need for ultracold infrastructure[25]. Leveraging saRNA technology (approved in India and Japan)[26], these vaccines can elicit robust immune responses at lower doses than conventional nucleoside-modified mRNA, potentially improving manufacturing efficiency and accessibility, particularly in settings with limited resources[27]. In addition to COVID-19 vaccines, an mRNA respiratory syncytial virus (RSV) vaccine[28] has recently been approved, highlighting the potential of mRNA platforms beyond COVID-19.

Infectious diseases

mRNA vaccines are being preclinically and clinically explored for infectious and combination infectious diseases, cancer immunotherapy, therapeutic protein replacement, and autoimmune disorders (Table 2), in particular, influenza, RSV, HIV, Zika, Ebola, rabies, malaria, tuberculosis and cytomegalovirus (CMV)[1,11,12,29–31]. Consistent with the 2025 US global-health strategy, which acknowledges the limitations of

Table 1 | Approved mRNA vaccines

Vaccine name	Developer	mRNA type	Immunogen	Approval region(s)
Comirnaty (BNT162b2)	Pfizer-BioNTech	Nucleoside-modified mRNA	COVID-19 (full-length spike)	USA (FDA), EU (EMA), UK (MHRA), Canada, Australia (TGA)
Spikevax (mRNA-1273)	ModernaTX	Nucleoside-modified mRNA	COVID-19 (full-length spike)	USA (FDA), EU (EMA), UK (MHRA), Canada, Australia (TGA)
AWcorna (ARCoV)	Walvax BiotechnologyAbogen Biosciences/PLA (AMMS)	Unmodified mRNA	COVID-19 (spike RBD)	Indonesia (Emergency Use Authorization)
Kostaive (ARCT-154)	Arcturus Therapeutics/CSL (Seqirus)	Self-amplifying mRNA	COVID-19 (full-length spike (D614G))	Japan (full approval), EU (EMA approval)
SYS6006	CSPC Pharmaceutical Group	Nucleoside-modified mRNA	COVID-19 (full-length spike)	China (Emergency Use Authorization)
Stemirna SW-BIC-213	Stemirna Therapeutics	Nucleoside-modified mRNA	COVID-19 (full-length spike)	China (Emergency Use Authorization)
GEMCOVAC-19	Gennova Biopharmaceuticals	Self-amplifying mRNA	COVID-19 (full-length spike)	India (Emergency Use Authorization)
GEMCOVAC-OM	Gennova Biopharmaceuticals	Self-amplifying mRNA	COVID-19 (full-length Omicron spike)	India (Emergency Use Authorization)
mNEXSPIKE (mRNA-1283)	ModernaTX	Nucleoside-modified mRNA	COVID-19 (spike RBD)	USA (FDA), EU (EMA)
mRESVIA (mRNA-1345)	ModernaTX	Nucleoside-modified mRNA	RSV (prefusion F protein)	USA (FDA), EU, UK (MHRA) Canada, Australia (TGA)

AMMS, Academy of Military Medical Sciences; EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency; PLA, People's Liberation Army; RBD, receptor-binding domain; RSV, respiratory syncytial virus; TGA, Therapeutic Goods Administration.

disease-specific silos and calls for integrated delivery platforms, bundling services across programmes can improve uptake and efficiency. Additionally, combination mRNA vaccines targeting multiple pathogens, such as COVID-19 and influenza, COVID-19 and RSV, COVID-19 and human papillomavirus (HPV), or COVID-19 and *Streptococcus pneumoniae*, and broader combinations, such as COVID-19, influenza and RSV, are being actively pursued[32]. These approaches aim to reduce injection burden, improve compliance and streamline immunization schedules, with multiple candidates demonstrating feasibility in clinical trials without compromising immunogenicity.

mRNA-based HIV vaccines remain in early-stage clinical trials[33–35], reflecting distinct challenges, such as the high mutation rate of HIV, glycan shielding and the need to induce rare broadly neutralizing antibodies[36]. In the IAVI G002 and G003 trials, which include cohorts in Africa, mRNA-encoded germline-targeting immunogens are used to activate VRC01-class broadly neutralizing antibody precursor B cells[37–39], resulting in rare precursor responses in 94–100% of participants[37]. These trials provide the first evidence that stepwise mRNA immunization can initiate broadly neutralizing antibody lineage maturation in humans. Although broadly neutralizing serum responses have not yet been achieved, reproducible priming and boosting support iterative immunogen strategies that may overcome prior vaccine limitations[33,34,36]. This mRNA platform further enables rapid antigen redesign and efficient expression of complex immunogens[30]. Although current trials remain in phase I, dosing, reactogenicity and sequential regimens are being optimized in follow-up studies[33].

Cancer

mRNA platforms are also explored for cancer immunotherapy[9,14,40], with multiple mRNA cancer vaccines advancing to phase I–III trials across various tumour types, including melanoma and pancreatic, colorectal, lung, head and neck, and prostate cancers[41,42]. Two major strategies have emerged: personalized neoantigen vaccines[43], which are tailored to the distinct mutations of an individual's tumour and target tumour-specific antigens, and shared antigen vaccines[42], which target tumour-associated antigens commonly expressed across patients[40]. Personalized approaches offer high specificity to a patient's tumour, whereas shared-antigen vaccines provide greater scalability and accessibility. The mRNA-4157 (V940) vaccine, combined with pembrolizumab, demonstrated a 44% reduction in recurrence risk in a phase IIb melanoma trial and has advanced to phase III (ref. 44). Here, next-generation sequencing was performed on individual tumours and blood samples. Tumour whole-exome sequencing was used to profile the mutanome (the entirety of the somatic cancer mutations of a tumour), whereas whole-exome sequencing of blood established each patient's human leukocyte antigen type. These data were then fed into an internal automated neoantigen-selection pipeline to design individualized mRNA-4157 vaccines (up to 34 neoantigen sequences per vaccine)[44]. Similarly, the autogene cevumeran (BNT122) vaccine has been associated with prolonged recurrence-free survival in patients with pancreatic cancer classified as responders, and is being tested in colorectal cancer[45,46]. For this vaccine, patient-specific neoantigens are derived from whole-exome sequencing of tumour–normal pairs and tumour RNA sequencing to identify expressed non-synonymous mutations; human leukocyte antigen typing is performed using DNA extracted from peripheral blood mononuclear cells. Candidate peptides are then computationally predicted and ranked for immunogenicity, and the top set is encoded in the individualized mRNA vaccine[45]. In addition, shared antigen mRNA vaccines, such as BNT111 (for melanoma), BNT113 (for HPV-positive head and neck cancer) and BNT116 (for lung cancers), have shown signs of immune activity and clinical benefit, particularly if combined with immune checkpoint inhibitors[47]. The modularity of mRNA platforms further enables integration with immunomodulators, cytokines, oncolytic viruses and chemotherapy, potentially enhancing therapeutic efficacy[48,49].

Therapeutics

mRNA platforms are being investigated for therapeutic protein delivery and immune modulation[8,16,50]. These therapies aim to deliver functional copies of mRNA encoding deficient or defective proteins, enabling

Table 2 | Ongoing clinical trials of mRNA vaccines

Immunogen	ClinicalTrials.gov identifier	Sponsor	Biological	Status
Influenza	NCT04956575 NCT05566639 NCT05415462 NCT05827978 NCT06602024 NCT05606965	ModernaTX	mRNA-1010	Phases I and II – completed Phase III – completed Phase III – completed Phase III – completed Phase III – active, not recruiting Phase II – recruiting
	NCT05540522	Pfizer	Quadrivalent influenza modRNA vaccine	Phase III – completed
	NCT06431607 NCT05823974	GlaxoSmithKline	GSK4382276A	Phase II – active, not recruiting Phases I and II – completed
	NCT05252338	CureVac	CVSQIV	Phase I – completed
	NCT06125691	Arcturus Therapeutics	ARCT-2138	Phase I – active, not recruiting
	NCT05227001	Pfizer	F-07852352 influenza saRNA	Phase I – completed
	NCT03076385	ModernaTX	VAL-506440	Phase I – completed
	NCT05333289	ModernaTX	mRNA-1030 mRNA-1020 mRNA-1010	Phases I and II – completed
	NCT03345043	ModernaTX	VAL-339851	Phase I – completed
	NCT05426174	Sanofi Pasteur, a Sanofi Company	Monovalent mRNA NA vaccine	Phase I – completed
	NCT05827068	ModernaTX	mRNA-1011.1 mRNA-1011.2 mRNA-1012.1 mRNA-1010 mRNA-1010.2 mRNA-1010.3	Phases I and II – completed
	NCT05868382	ModernaTX	mRNA-1010 mRNA-1010.4 mRNA-1010.6	Phase II – completed
	NCT06028347	Seqirus	saRNA vaccine	Phase I – completed
	NCT05829356	Sanofi Pasteur, a Sanofi Company	H3 mRNA–LNP vaccine	Phase I – completed
	NCT05650554	Sanofi Pasteur, a Sanofi Company	Quadrivalent influenza mRNA vaccine MRT5413	Phases I and II – completed
	NCT05553301	Sanofi Pasteur, a Sanofi Company	Quadrivalent influenza mRNA vaccine MRT5407	Phases I and II – completed
	NCT03814720	National Institute of Allergy and Infectious Diseases (NIAID)	VRC-FLUNPF099-00-VP (H1ssF_3928)	Phase I – completed
	NCT05446740	GlaxoSmithKline	GSK4382276A dose level 1 to 11	Phase I – completed
CMV	NCT05085366 NCT05683457 NCT04232280 NCT05105048	ModernaTX	mRNA-1647	Phase III – active, not recruiting Phase II – recruiting Phase II – completed Phase I – completed
	NCT03382405	ModernaTX	mRNA-1647 mRNA-1443	Phase I – completed
Zika	NCT03014089	ModernaTX	mRNA-1325	Phase I – completed
	NCT04064905 NCT04917861	ModernaTX	mRNA-1893	Phase I – completed Phase II – completed
Herpes Zoster	NCT05871541	Immorna Biotherapeutics	JCXH-105	Phase I – completed
Tuberculosis	NCT05547464	BioNTech	BNT164 (BNT164a1 and BNT164b1)	Phases I and II – recruiting

Table 2 (continued) | Ongoing clinical trials of mRNA vaccines

Immunogen	ClinicalTrials.gov identifier	Sponsor	Biological	Status
Malaria	NCT06069544	BioNTech	BNT165e	Phases I and II – active, not recruiting
	NCT05581641	BioNTech	BNT165b1	Phase I – completed
Norovirus	NCT05992935 NCT06592794	ModernaTX	mRNA-1403 and mRNA-1405 mRNA-1403	Phases I and II – active, not recruiting Phase III – active, not recruiting
Nipah virus	NCT05398796	NIAID	mRNA -1215	Phase I – completed
HSV-2 genital herpes	NCT05432583	BioNTech	BNT163	Phase I – recruiting
	NCT06033261	ModernaTX	mRNA-1608	Phases I and II – completed
Rabies	NCT04062669	GlaxoSmithKline	GSK3903133A	Phase I – completed
	NCT03713086	CureVac	CV7202	Phase I – completed
	NCT02241135	CureVac	CV7201	Phase I – completed
Chikungunya	NCT03325075	ModernaTX	VAL-181388	Phase I – completed
EBV	NCT05831111	ModernaTX	mRNA-1195	Phase I – recruiting
Lyme disease	NCT05975099	ModernaTX	mRNA-1975 mRNA-1982	Phases I and II – active, not recruiting
COVID-19 and influenza	NCT05375838	ModernaTX	mRNA-1073 mRNA-1010 mRNA-1273	Phases I and II –completed
	NCT05827926 NCT06097273 NCT06864143 NCT06694389	ModernaTX	mRNA-1083	Phases I and II – completed Phase III – completed Phase II – recruiting Phase III – active, not recruiting
	NCT06178991 NCT05596734	BioNTech	Influenza and COVID-19 combination A Bivalent BNT162b2 (original/Omi BA.4/BA.5)	Phase III – completed Phases I and II – completed
	NCT06680375	GlaxoSmithKline	Flu Seasonal/SARS-CoV-2 mRNA (mRNA Flu/COVID-19)	Phases I and II – active, not recruiting
	NCT04969276	Sanofi Pasteur, a Sanofi Company	Quadrivalent inactivated influenza high dose COVID-19 mRNA vaccine (nucleoside modified)	Phase II – completed
	NCT05970887	Catholic Kwandong University	Bivalent BNT162b2 mRNA original/omicron BA.4-5 vaccine Quadrivalent influenza vaccine	Phase IV – completed
COVID-19 and influenza and RSV	NCT05585632	ModernaTX	mRNA-1010 mRNA-1345 mRNA-1273.214 mRNA-1045 mRNA-1230	Phase I – completed
	NCT05330975	ModernaTX	mRNA-1345 mRNA-1273.214 Afluria Quadrivalent	Phase III – completed
COVID-19 and RSV	NCT05886777	Pfizer	Combination (RSVpreF+BNTb162b2)	Phase II – completed
COVID-19 and HPV	NCT05119855	Merck Sharp & Dohme	9vHPV vaccine mRNA-1273	Phase III – completed
COVID-19 and *Streptococcus pneumoniae*	NCT05158140	Merck Sharp & Dohme	mRNA-1273 V110 and V114	Phase III – completed
	NCT04887948	Pfizer	BNT162b2 20-valent pneumococcal conjugate vaccine (20vPnC)	Phase III – completed
Influenza and RSV	NCT05788237	Pfizer	RSVpreF+qIRV	Phase I – completed
	NCT06060457	ModernaTX	mRNA-1345 Fluzone HD	Phase III – completed

Table 2 (continued) | Ongoing clinical trials of mRNA vaccines

Immunogen	ClinicalTrials.gov identifier	Sponsor	Biological	Status
Human metapneumovirus and human parainfluenza virus type 3	NCT03392389 NCT04144348	ModernaTX	mRNA-1653	Phase I – completed Phase I – completed
HIV	NCT06557785	NIAID	CH505M5 N197D mRNA-gp160 CH505 TF mRNA-gp160	Phase I – recruiting
	NCT05217641	NIAID	BioBG505 MD39.3 mRNA BG505 MD39.3 gp151 mRNA BG505 MD39.3 gp151 CD4KO mRNA	Phase I – active, not recruiting
	NCT05001373	International AIDS Vaccine Initiative	eOD-GT8 60-mer mRNA vaccine (mRNA-1644) Core-g28v2 60-mer mRNA vaccine (mRNA-1644v2-Core)	Phase I – active, not recruiting
	NCT05414786	International AIDS Vaccine Initiative	eOD-GT8 60-mer mRNA vaccine (mRNA-1644)	Phase I – unknown
	NCT05903339	NIAID	V3G CH848 mRNA-Tr2	Phase I – active, not recruiting
Cancer (personalized neoantigen-based vaccine)	NCT03313778 NCT03897881	ModernaTX	mRNA-4157 Pembrolizumab	Phase I – recruiting Phase II – recruiting
	NCT06077760 NCT06623422 NCT06961006 NCT06833073 NCT06305767 NCT06307431 NCT05933577 NCT06295809 NCT03897881	Merck Sharp & Dohme	V940 (mRNA-4157) plus pembrolizumab	Phase III – recruiting Phase III – recruiting Phase II – recruiting Phase II – recruiting Phases I and II – recruiting Phase II – active, not recruiting Phase III – active, not recruiting Phases II and III – active, not recruiting Phase II – recruiting
	NCT02316457	BioNTech	IVAC_W_bre1_uID	Phase I – completed
	NCT04486378	BioNTech	BNT122-01	Phase II – recruiting
	NCT03289962 NCT03815058 NCT05968326	Genentech	Autogene cevumeran Atezolizumab mFOLFIRINOX	Phase I – completed Phase II – completed Phase II – recruiting
	NCT04161755	Memorial Sloan Kettering Cancer Center	Atezolizumab RO7198457 mFOLFIRINOX	Phase I – active, not recruiting
	NCT06195384	Second Affiliated Hospital of Guangzhou Medical University	Anti-cancer neoantigen mRNA vaccine to treat solid tumours	Phase I – recruiting
	NCT06932861	Chinese PLA General Hospital	mRNA tumour vaccine therapy	Early phase I – not yet recruiting
	NCT06156267	Fudan University	mRNA tumour vaccine Adebrelimab	Early phase I – not yet recruiting
	NCT06496373	Ruijin Hospital	XP-004 personalized mRNA vaccine combined with PD-1 inhibitor	Early phase I – recruiting
Cancer (shared antigen mRNA vaccines)	NCT04534205	BioNTech	BNT113	Phases II and III – recruiting
	NCT05142189	BioNTech	BNT116	Phase I – recruiting
	NCT07004244	Sichuan University	KRAS-mutated mRNA vaccine Toripalimab	Phase I – recruiting
	NCT06577532	Ruijin Hospital	mRNA nanoparticles encoding KRAS neoantigens (ABO2102) Toripalimab	Early phase I – recruiting
	NCT05533697	ModernaTX	mRNA-4359 pembrolizumab	Phases I and II – recruiting
	NCT05938387	CureVac	CV09050101 mRNA vaccine (CVGBM)	Phase I – active, not recruiting
	NCT05714748	West China Hospital	EBV mRNA vaccine	Phase I – active, not recruiting
	NCT07053072	West China Hospital	PD-1 mRNA–LNP vaccine	Phases I and II – not yet recruiting
	NCT03948763	Merck Sharp & Dohme	mRNA-5671/V941	Phase I – terminated

Table 2 (continued) | Ongoing clinical trials of mRNA vaccines

Immunogen	ClinicalTrials.gov identifier	Sponsor	Biological	Status
Propionic acidaemia	NCT05130437 NCT04159103	ModernaTX	mRNA-3927	Phases I and II – recruiting Phases I and II – recruiting
Isolated methylmalonic acidaemia	NCT05295433 NCT04899310	ModernaTX	mRNA-3705	Phases I and II – recruiting Phases I and II – recruiting
Propionic acidaemia or methylmalonic acidaemia	NCT05769621	ModernaTX	mRNA-3927-P002	Observational – active, not recruiting
Glycogen storage disease type 1a	NCT05095727	ModernaTX	mRNA-3745-P102	Phases I and II – recruiting
Cystic fibrosis	NCT05712538 NCT06747858	Arcturus Therapeutics	ARCT-032	Phase I – completed Phase II – recruiting
	NCT06237335	ReCode Therapeutics	RCT2100	Phase I – recruiting
	NCT03375047	Translate Bio	MRT5005	Phases I and II – unknown
Ornithine transcarbamylase deficiency	NCT04442347 NCT05526066	Arcturus Therapeutics	ARCT-810	Phase I – completed Phase II – terminated
Chronic heart failure	NCT05659264	ModernaTX	mRNA-0184	Phase I – completed
Multiple sclerosis	NCT06735248	ModernaTX	mRNA-1195	Phase II – recruiting
Autoimmune diseases (Treg expansion via IL-2 mutein)	NCT04916431	ModernaTX	mRNA-6231	Phase I – completed
Therapeutic mRNA antibody production	NCT05262530	BioNTech	BNT142	Phase I – active, not recruiting
Immunomodulatory proteins (cytokines)	NCT03739931	ModernaTX	mRNA-2752	Phase I – active, not recruiting
	NCT03323398	ModernaTX	mRNA-2416	Phases I and II – terminated
	NCT03946800	MedImmune	MEDI1191 Durvalumab	Phase I – completed
Immunostimulatory mRNA therapeutic	NCT03739931	ModernaTX	mRNA-2752 Durvalumab	Phase I – active, not recruiting

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; IL-2, interleukin-2; LNP, lipid nanoparticles; PD-1, programmed cell death protein 1; PLA, People's Liberation Army; RSV, respiratory syncytial virus; NA, neuraminidase; saRNA, self-amplifying RNA; Treg, regulatory T cell.

in situ protein production to restore physiological function[7,50]. Currently, clinical trials are underway for rare genetic and metabolic disorders, including trials with mRNA-3927 (propionic acidaemia)[51,52], mRNA-3705 (methylmalonic acidaemia)[53] and mRNA-3745 (glycogen storage disease type Ia)[16]. These candidates have demonstrated acceptable safety and early biomarker responses, although long-term efficacy remains under evaluation. Moreover, inhaled mRNA therapies are tested for the treatment of cystic fibrosis; for example, ARCT-032 showed initial safety and modest lung function improvement in a patient with class I mutation[54], the trial on RCT2100 is now recruiting in phase II, and MRT5005 demonstrated safety but lacked consistent clinical benefit[55]. Although mRNA therapeutics for protein replacement remain in early clinical development, they have shown promising safety and feasibility.

Clinical progress in mRNA therapeutics for autoimmune diseases remains limited[56,57], with only one clinical trial recruiting for phase II for testing mRNA-1195 in multiple sclerosis. However, several strategies are being preclinically explored that induce antigen-specific tolerance, particularly in diseases such as multiple sclerosis, type 1 diabetes[58,59] and rheumatoid arthritis. For example, a tolerogenic mRNA platform based on nucleoside-modified (m1Ψ) mRNA encoding myelin antigens, which is complexed with liposomes that lack inherent adjuvant activity, has shown efficacy in experimental autoimmune encephalomyelitis models of multiple sclerosis[60]. Similarly, mRNA vaccines, encoding tandem glutamic acid decarboxylase 65 (GAD65) epitopes and cholera toxin B subunit (CTB-GADIII), reduce type 1 diabetes incidence, delay disease progression, improve glucose tolerance and protect pancreatic morphology in non-obese diabetic mice, accompanied by modulation of $CD4^+$ T cell subsets and increased interleukin (IL)-10 and transforming growth factor beta (TGFβ) levels in serum, suggesting the possible mechanism of immune tolerance[59]. mRNA-induced programmed death ligand 1 (PDL1) expression on antigen-presenting cells has shown promise by reducing the fraction of activated T cells, promoting the induction of regulatory T cells and preventing disease progression in preclinical rheumatoid arthritis models[61]. In addition, mRNA-6231, encoding a modified IL-2 fused to human serum albumin, can drive regulatory T cell expansion in nonhuman primates[62]. A completed phase I trial in healthy volunteers demonstrated safety and pharmacodynamic activity, including regulatory T cell expansion[62]; however, the programme was discontinued following phase I results and portfolio reprioritization. Therefore, LNP-formulated mRNA can reprogram autoreactive immune cells and restore tolerance without broad immunosuppression[60] in preclinical models.

mRNA platforms are also being developed for therapeutic immune modulation[63]. These approaches rely on in vivo expression of

immunomodulatory proteins, such as cytokines (IL-12, IL-23 and IL-36γ), co-stimulatory ligands (OX40L) or tolerogenic antigens, to reprogram immune responses in autoimmunity, inflammation and cancer[64,65]. Several candidates have entered clinical trials for cancer immunotherapy (Table 2), including mRNA-2416, mRNA-2752 and MEDI1191, all delivered intratumourally[49,66]. Unlike vaccines, these approaches aim to modulate local immunity rather than induce long-term immune memory.

Technical, economical and logistical barriers to accessibility

The development, production and deployment of mRNA vaccines involve several interconnected steps, including DNA template design, DNA production and purification, in vitro transcription and mRNA purification, encapsulation in LNPs, and packaging and distribution[16,67] (Fig. 1). Each stage presents technical, economic and logistical challenges that collectively limit accessibility, with regulatory barriers adding further complexity. Such barriers might be addressed by enhancing funding for cross-disciplinary research collaborations, expanding shared informatics infrastructure and fostering academic–industry partnerships[68].

Design of DNA template sequence

The first step in the production of mRNA vaccines involves the design of a DNA template optimized for stability, translation efficiency and low immunogenicity[69]. Essential components include a promoter sequence, an open reading frame encoding the gene of interest, 5′ and 3′ untranslated regions (UTRs), and a poly(A) tail[6,12]. A central technical bottleneck is an incomplete, quantitative understanding of how coding sequences, UTRs, RNA structure and modifications determine stability, translation and innate immune sensing. Many of these considerations were first explored in the context of DNA vaccination studies in the 1990s. Technical challenges include selecting and optimizing these elements, performing codon and GC-content optimization to enhance mRNA stability and translation efficiency, and tailoring UTR sequences to maximize protein expression[6]. Such design processes require advanced bioinformatics expertise and computational resources[70], which can be costly and not universally accessible. Artificial intelligence (AI) and machine learning might be leveraged to optimize sequence design[71–73]. In addition, shared bioinformatics hubs and open-source Encyclopedia of DNA Elements (ENCODE)-like databases of RNA elements could be established to accelerate benchmarking and learning.

Production and purification of DNA template

Producing and purifying DNA templates require high yield, purity and consistency while preventing contamination[74]. Templates can be plasmid DNA, polymerase chain reaction (PCR)-amplified products or synthetic double-stranded oligonucleotides, each presenting distinct production challenges[6,74,75]. For example, plasmid-based templates require antibiotic-resistance markers and specific linearization sites for bacterial propagation and template processing. DNA templates for therapeutic mRNA production are typically several kilobases in length, and, therefore, bacterial fermentation-based plasmid DNA production currently represents the most commonly used approach. Importantly, specialized manufacturing facilities, as well as costly reagents and raw materials, are typically needed. Additionally, DNA templates must be purified and linearized prior to in vitro transcription. Costs could be reduced by developing efficient bacterial or cell-free amplification techniques, as well as automation technologies to ensure consistency and scalability.

In vitro transcription and mRNA purification

mRNA is then usually enzymatically synthesized by in vitro transcription, typically using T7 RNA polymerase, nucleotide triphosphates, magnesium ions and optimized buffers[7,8,16]. However, these specialized enzymes and reagents are expensive and have limited availability. Moreover, the reaction conditions need to be tightly controlled to minimize the formation of immunogenic double-stranded RNA (dsRNA) by-products[6,7]. Not only do these contaminants complicate purification, but they also raise safety concerns. Purification must remove residual DNA, enzymes, unincorporated nucleotide triphosphates, truncated transcripts and dsRNA[50,76,77]. Although methods such as high-performance liquid chromatography and oligo-dT affinity chromatography are effective, they are technically demanding, costly and difficult to scale[78]. Engineered RNA polymerases could limit by-product formation. In addition, complexity, costs and contamination risk could be reduced by developing cost-effective purification methods and improved reagents, and by integrating automation and continuous manufacturing.

Encapsulation of mRNA in LNP formulations

Encapsulation in LNPs is essential for mRNA stability, protection from degradation and efficient cellular uptake[6,10]. LNPs typically comprise ionizable lipids, phospholipids, cholesterol and PEG lipids[9,10,79], with formulation and component ratios influencing particle size, encapsulation efficiency, stability, biodistribution and immunogenicity[80]. Microfluidic mixing has become the standard for scalable LNP production, enabling controlled and reproducible nanoparticle formation[81]. However, these systems require specialized, costly equipment and good manufacturing practice (GMP)-compliant infrastructure, limiting deployment in decentralized or resource-limited settings[16,82]. Additional barriers include maintaining batch consistency, achieving high encapsulation efficiency, preventing aggregation and the high cost of proprietary ionizable lipids[80]. To improve accessibility, less expensive lipid sources or synthetic methods could be developed for LNP formulation, in addition to adopting cost-effective and modular production technologies, using automation to reduce variability, and exploring new excipients or formulations that enhance long-term stability and facilitate easier storage and transport.

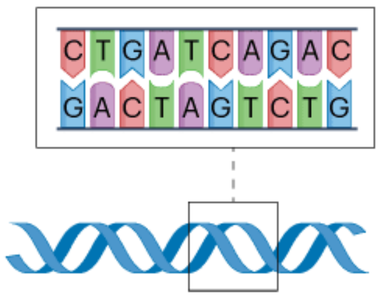
Packaging and distribution

Product sterility, stability and potency must be ensured during packaging, storage and global distribution[16]. However, maintaining sterile conditions, controlling temperature throughout transportation and ensuring timely delivery remain difficult, particularly in resource-limited settings[83]. Additional economic and logistical complexities result from the high cost of sterile packaging materials, specialized filling equipment, and cold-storage and distribution infrastructure, all of which limit equitable global access[6,84]. Accessibility could be improved by developing thermostable mRNA formulations, adopting cost-effective and single-use filling technologies, automating precision packaging with robotic systems, using smart monitoring technologies for real-time temperature control, establishing decentralized production and distribution hubs to reduce reliance on cold chains, strengthening regional distribution networks, and simplifying vaccine administration through delivery methods such as microneedle patches[85–87].

Regulatory challenges

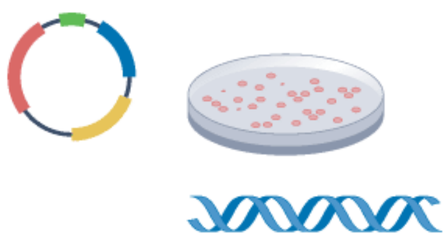
The regulation of mRNA vaccines presents a complex set of challenges spanning manufacturing quality, approval pathways and long-term

a Design of DNA template sequence



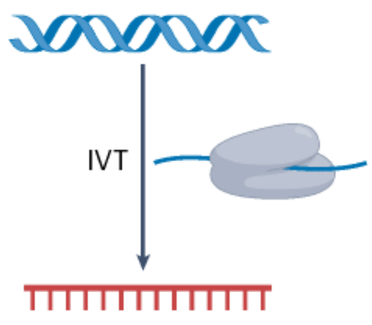
Technical barrier	Logistical barrier	Economical barrier	Potential solutions
Requirement for advanced bioinformatics approaches to optimize sequence features governing stability, translation efficiency and immunogenicity	Limited access to computational and specialized bioinformatics tools	High costs associated with developing and maintaining specialized computational pipelines and licensing proprietary software	• AI-guided and ML-guided sequence optimization • Open and shared bioinformatics platforms with standardized pipelines • Publicly available sequence datasets

b Production and purification of the DNA template



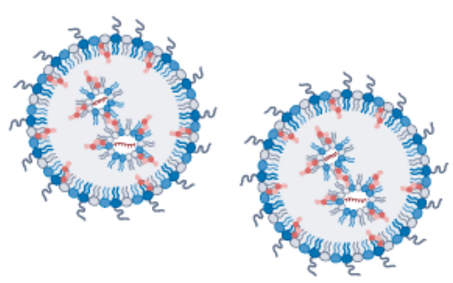
Maintaining high yield and purity while minimizing mutations and contamination	Scaling up production while maintaining batch-to-batch consistency; limited access to specialized manufacturing infrastructure	High costs associated with raw materials and specialized production facilities	• Scalable bacterial or cell-free DNA amplification • Automated production and purification workflows

c In vitro transcription and mRNA purification



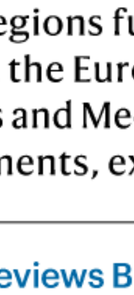
Achieving high mRNA yield and integrity while minimizing dsRNA impurities and enzymatic inefficiencies	Ensuring reproducible and contamination-free IVT and purification workflows at scale	High costs associated with enzymes, reagents and purification materials, particularly for large-scale production	• Engineered RNA polymerases to reduce formation of dsRNA • Scalable and efficient mRNA purification strategies • Optimized IVT reagents, including modified nucleotides, and advanced capping chemistries • Automation of IVT and purification workflows to improve reproducibility and reduce contamination risk

d Encapsulation of mRNA in LNP formulations



Optimizing lipid composition and formulation parameters to achieve stable nanoparticles with high mRNA encapsulation, controlled release and efficient cellular uptake	Requirement for GMP-compliant infrastructure, and achieving reproducible LNP formulation and scale-up while maintaining particle key quality attributes across batches	High costs associated with specialized lipids and nanoparticle components, as well as GMP-compliant manufacturing infrastructure	• Alternative and modular lipid sources to reduce cost and supply constraints • Cost-effective synthesis and scale-up of ionizable and helper lipids • Automated LNP formulation processes to improve reproducibility and scalability • AI-guided and ML-guided design and optimization of lipid composition and formulation parameters

e Packaging and distribution



Maintaining sterility and product stability while preventing contamination and temperature changes during distribution	Cold-chain logistics requiring continuous temperature monitoring, specialized equipment and coordinated distribution	High costs associated with sterile packaging materials, cold storage and transportation infrastructure, and supply-chain operations	• Thermostable mRNA formulations • Single-use filling and packaging systems • Robotic and automated aseptic handling • Decentralized or regional distribution hubs • Simplified delivery formats enabled by packaging (such as pre-filled syringes or microneedle patches)

Fig. 1 | Barriers to mRNA vaccine development and manufacturing. Technical, logistical and economic challenges and potential solutions across five major steps in mRNA vaccine development: DNA template design (part **a**), DNA production and purification (part **b**), in vitro transcription and mRNA purification (part **c**), mRNA encapsulation in lipid nanoparticles (LNPs) (part **d**), and packaging and distribution (part **e**). AI, artificial intelligence; dsRNA, double-stranded RNA; GMP, good manufacturing practices; IVT, in vitro transcription; ML, machine learning.

oversight[88]. A key concern is ensuring manufacturing consistency, particularly the ability to maintain high purity, potency, stability and batch-to-batch reproducibility at scale[89,90]. This requires robust quality control systems[91], including validated analytical assays for identity, integrity and impurity removal, as well as real-time monitoring during production[92]. Variability in regulatory expectations across regions further complicates licensure[90]. Agencies such as the FDA, the European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency (PMDA) differ in clinical trial requirements, expedited approval pathways and post-marketing surveillance practices, leading to fragmented global development efforts[93] (Table 3).

Harmonizing global regulatory pathways

Global regulatory harmonization has become a growing priority following the COVID-19 pandemic[89,94], particularly to streamline the approval of mRNA vaccines and enable timely, equitable access worldwide[95]. Fragmented regulatory requirements, ranging from clinical trial design to post-marketing surveillance, can delay vaccine rollout, increase costs and complicate global access[96]. Limited

Table 3 | Global regulatory requirements for mRNA vaccines

Regulatory body	Preclinical requirements	Clinical trial phases	Expedited pathways	Full approval	Post-marketing surveillance
FDA (USA)	In vitro and animal studies, CMC data	Phases I–III IND required	Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review, EUA (for public-health emergencies)	BLA approval (FDA/CBER), Advisory Committee Review (VRBPAC) convened as needed	Phase IV, FDA-CDC safety surveillance (such as VAERS and VSD monitoring)
EMA (Europe)	In vitro and animal studies, CMC data	Phases I–III CTA required	PRIME, CMA, Accelerated Assessment, Rolling review (emergency procedure)	EC marketing authorization following CHMP review	Phase IV, EudraVigilance with PRAC oversight, PASS as required
MHRA (UK)	In vitro and animal studies, CMC data	Phases I–III CTA required	Rolling Review, CMA, temporary authorization for emergency supply	Marketing authorization (standard or conditional) granted by MHRA	Phase IV, Yellow Card Scheme
PMDA (Japan)	In vitro and animal studies, CMC data	Phases I–III CTN required	Sakigake, Conditional Early Approval, Priority Review	MHLW marketing authorization following PMDA review	Phase IV, JADER database, re-examination, including PSURs, RMP
NMPA (China)	In vitro and animal studies, CMC data	Phases I–III CTA required	Priority Review, Breakthrough Therapy, Conditional Approval, Special Approval	Marketing authorization by NMPA, vaccines subject to lot release by NIFDC	Phase IV, national AEFI surveillance (CNAEFIIS)
TGA (Australia)	In vitro and animal studies, CMC data	Phases I–III CTN or CTA (as applicable)	Provisional registration, priority review	TGA registration via standard or priority pathways, provisional can transition to full registration	Phase IV, DAEN (passive) and AusVaxSafety (active) surveillance
CDSCO (India)	In vitro and animal studies, CMC data (NDCTR) framework	Phases I–III, clinical trial permission required under NDCTR	Accelerated approval (NDCTR), restricted emergency use with regulatory reliance (such as WHO's EUL, FDA/EMA/MHRA/PMDA)	New drug permission/ marketing authorization by CDSCO/DCGI, vaccine lot-by-lot release by CDL	Phase IV, PvPI and National AEFI surveillance, periodic safety reporting per CDSCO guidance
National authorities (such as SAHPRA (South Africa), NAFDAC (Nigeria) and Food and Drugs Authority (Ghana), coordinated by AMA (Africa))	In vitro and animal studies, CMC/quality requirement per NMRA, AVAREF supports joint review for multi-country studies	Phases I–III with national CTA, AVAREF offers regular, expedited and emergency joint reviews	Regulatory reliance mechanisms commonly applied (such as WHO's CRP, WHO's EUL, reliance on SRA assessments)	Marketing authorization by NMRA, abridged or verification reviews using WHO's CRP and prequalification SRA reports	Phase IV, national pharmacovigilance and AEFI surveillance (such as VigiBase reporting, Med Safety app, NMRA-specific guidelines)

Breakthrough Therapy is FDA's designation for drugs showing substantial improvement. Conditional Approval is an approval granted with conditions, pending more data. EudraVigilance is the EMA's system for managing and analysing adverse event reports. Fast Track is the FDA's pathway to expedite review of drugs for serious conditions. Sakigake is a fast-track approval system in Japan for innovative medicines. Yellow Card Scheme is MHRA's post-market surveillance in the UK. VigiBase is the WHO's global database of individual case safety reports. AEFI, adverse event following immunization; AMA, African Medicines Agency; AVAREF, African Vaccine Regulatory Forum; BLA, Biologics License Application; CBER, Center for Biologics Evaluation and Research; CDC, Centers for Disease Control and Prevention; CDL, Central Drugs Laboratory; CDSCO, Central Drugs Standard Control Organization; CHMP, Committee for Medicinal Products for Human Use; CMA, Conditional Marketing Authorisation; CMC, Chemistry, Manufacturing, and Controls; CNAEFIS, Chinese National Adverse Events Following Immunization Information System; CRP, Collaborative Registration Procedure; CTA, Clinical Trial Application (EMA/MHRA/TGA); CTN, Clinical Trial Notification; DAEN, Database of Adverse Event Notifications; DCGI: Drugs Controller General of India; EC, European Commission; EMA, European Medicines Agency; EUA, Emergency Use Authorization; EUL, Emergency Use Listing; FDA, US Food and Drug Administration; IND, Investigational New Drug application; JADER, Japanese Adverse Drug Event Report; MHLW, Ministry of Health, Labour and Welfare; MHRA, Medicines and Healthcare products Regulatory Agency; NAFDAC, National Agency for Food and Drug Administration and Control; NDCTR: New Drugs and Clinical Trials Rules; NIFDC, National Institutes for Food and Drug Control; NMPA, National Medical Products Administration; NMRA, National Medicines Regulatory Authority; PASS, post-authorisation safety studies; PMDA, Pharmaceuticals and Medical Devices Agency; PRAC, Pharmacovigilance Risk Assessment Committee; PRIME, Priority Medicines; PSURs, Periodic Safety Update Reports; PvPI, Pharmacovigilance Programme of India; RMP, Risk Management Plan; SAHPRA, South African Health Products Regulatory Authority; SRA, Stringent Regulatory Authority; TGA, Therapeutic Goods Administration; VAERS, Vaccine Adverse Event Reporting System; VRBPAC, Vaccines and Related Biological Products Advisory Committee; VSD, Vaccine Safety Datalink; WHO, World Health Organization.

harmonization of immunogenicity and safety end points slows down multinational trials and complicates data interpretation, whereas globally harmonized guidelines for trial design, clinical end points and safety assessments can streamline approvals and reduce redundancies[16,90,97]. The success of Operation Warp Speed, a public–private partnership to facilitate and accelerate the development, manufacturing and distribution of COVID-19 vaccines, demonstrates that shared clinical frameworks, centralized data monitoring, and parallel investments in manufacturing and trials can accelerate vaccine development without compromising regulatory rigor or public trust[98]. Key elements include convergence on trial protocols, mutual recognition of GMP inspections and safety data, and adoption of shared technical standards[99]. Strengthening long-term safety monitoring through real-world evidence and robust pharmacovigilance networks remains essential beyond initial authorization[97].

Multiple international initiatives have emerged to align standards and implement reliance mechanisms (Table 4). Organizations such as the International Coalition of Medicines Regulatory Authorities (ICMRA) and the International Council for Harmonisation (ICH) are leading efforts to standardize trial protocols, safety reporting, GMP and pharmacovigilance standards[100]. The World Health Organization (WHO)'s Collaborative Registration Procedure (CRP) and Emergency Use Listing (EUL) enable low- and middle-income countries (LMICs) to leverage assessments from stringent regulatory authorities, as parallel review programmes, such as Project Orbis, facilitate coordinated evaluations across agencies, including the FDA, EMA, PMDA, Medicines and Healthcare products Regulatory Agency (MHRA) and Therapeutic Goods Administration (TGA)[101–103]. Joint parallel review models, such as Project Orbis, have accelerated the time to approval in real-world implementation; for example, participation by Swissmedic reduced submission gaps from a median of ~168 days to ~33 days and shortened review times by several weeks, with high concordance in regulatory decisions across agencies[101]. Mutual Recognition Agreements, such as those between the EMA and FDA, further reduce redundancy in GMP inspections and foster regulatory trust. Efforts to decentralize vaccine manufacturing, such as the WHO's mRNA technology transfer hub in South Africa, are supported by regional regulatory convergence and capacity building[104,105].

Global health partnerships, including Gavi, the Vaccine Alliance, CEPI and the COVID-19 Vaccines Global Access (COVAX) facility, have supported regulatory streamlining through coordinated procurement, technical assistance and dose-sharing mechanisms[20]. Region-specific efforts, such as the African Vaccine Regulatory Forum (AVAREF) and the newly launched African Medicines Agency (AMA), are working to harmonize regulatory frameworks and strengthen oversight capacity across the continent[106–109].

However, regulatory approval alone is insufficient for equitable vaccine access, which also depends on manufacturing capacity, affordability, fair allocation and efficient deployment[84]. Improving global coordination, sharing technical guidance and ensuring transparent monitoring of vaccine candidates could further promote equity[84]. To future-proof regulatory systems for mRNA vaccines, policies must also adapt to emerging technologies, such as thermostable formulations, cold-chain innovations and decentralized manufacturing. For example, a portable printer-based platform allows on-site fabrication of thermostable microneedle vaccines, highlighting a pathway to improve accessibility during pandemics[86]. Finally, transparent communication and public engagement remain crucial to sustaining public confidence[110].

Challenges in achieving full harmonization

Despite progress towards harmonizing global regulatory pathways for mRNA-vaccine approval, several challenges remain[84,95]. A key obstacle is the variation in national regulations and data requirements, which makes it difficult to establish a universally accepted approval framework[84,97]. Although regulatory authorities such as

Table 4 | Harmonizing regulatory pathways for mRNA Vaccines

Initiative	Description
International Coalition of Medicines Regulatory Authorities (ICMRA)	Voluntary coalition of national medicines regulatory authorities that facilitates global regulatory cooperation, information sharing and coordinated responses to emerging public health and safety challenges
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)	Develops harmonized technical guidelines for quality, safety, efficacy and multidisciplinary aspects of medicinal products through regulatory authorities and collaboration with the pharmaceutical industry
World Health Organization's (WHO) Collaborative Registration Procedure (CRP)	Facilitates accelerated national registration through regulatory reliance on assessment and GMP inspection reports from Stringent Regulatory Authorities, using recognition or abridged review pathways
World Health Organization's (WHO) Emergency Use Listing (EUL)	Provides time-limited emergency assessment of unlicensed vaccines to support UN procurement and national regulatory reliance during public-health emergencies
Project Orbis	FDA-led international regulatory collaboration enabling concurrent submission and collaborative review of oncology products across participating regulatory authorities to accelerate patient access
Mutual Recognition Agreements (MRAs)	Enables mutual recognition of GMP inspection outcomes between regulatory authorities, reducing duplication and supporting global manufacturing oversight and supply continuity (such as FDA–EU, FDA–UK)
WHO mRNA Technology Transfer Hub	WHO-supported mRNA hubs (led by Afrigen in South Africa) aiming to harmonize regulatory standards by transferring platform data for aligned approvals; enables regional mRNA vaccine manufacturing through technology transfer, workforce training and shared production processes
Gavi, the Vaccine Alliance	Public–private partnership that expands access to vaccines in low-income and middle-income countries through financing, pooled procurement and market-shaping mechanisms, relying on WHO regulatory approvals
COVID-19 Vaccines Global Access (COVAX)	Multilateral COVID-19 vaccine development, procurement and access mechanism (2020–2023), co-led by Gavi, the Vaccine Alliance, CEPI, WHO and UNICEF, relying on WHO regulatory pathways
Coalition for Epidemic Preparedness Innovations (CEPI)	Global funder that supports vaccine research and development to accelerate availability of vaccines for epidemic and pandemic threats
African Vaccine Regulatory Forum (AVAREF)	WHO-coordinated platform that enables joint review of vaccine clinical trial applications and regulatory collaboration among African national regulatory authorities
African Medicines Agency (AMA)	African Union agency coordinating continental regulatory harmonization through joint reviews, joint inspections and information sharing among national medicines regulatory authorities

FDA, US Food and Drug Administration; GMP, good manufacturing practice; EU, European Union.

the FDA and EMA apply stringent efficacy and safety criteria[111], others may prioritize different end points or follow distinct clinical trial designs[112]. Public-health policies and political priorities further shape regulatory decisions, influencing the pace and flexibility of vaccine authorizations[113]. For example, some regions expedite approvals during health emergencies, whereas others adhere to more cautious, prolonged review timelines[101–103]. Another challenge is the need for region-specific post-marketing surveillance[114]. Owing to genetic diversity, as well as differences in healthcare infrastructure, disease burden and immunogenicity, adverse event profiles might vary across regions, requiring localized pharmacovigilance systems rather than a one-size-fits-all approach[98]. Countries without national regulatory agencies often rely on approvals granted by stringent regulatory authorities such as the FDA or EMA, which can delay independent decision-making and create dependencies.

The evolving nature of mRNA technologies presents an additional layer of complexity[78]. For multivalent or multi-pathogen mRNA vaccines, regulators generally treat the product as a new combination vaccine, requiring evidence that each antigen remains safe and immunogenic in the co-formulation (without immune interference), alongside antigen-specific potency and quality assays, and, when appropriate, clinical bridging to monovalent comparators. The development of new technologies, such as thermostable formulations, saRNA or alternative delivery systems (for example, microneedles or dry powders), often outpace existing regulatory frameworks. Expedited mechanisms, such as Emergency Use Authorization, the EMA's Priority Medicines (PRIME) and Japan's Sakigake designation, can offer early access to promising vaccines but require careful calibration between speed and scientific rigor[115].

Cold-chain requirements remain both a regulatory and logistical barrier, and lyophilized or room-temperature-stable products demand updated stability standards and assessment protocols[116]. Transparent public communication around regulatory decisions, efficacy outcomes and adverse event reporting is essential to maintaining public trust in mRNA-vaccine platforms[117,118]. To address these challenges, a multifaceted and adaptive regulatory approach is needed[119]. Work-sharing models, mutual recognition agreements and reliance pathways can reduce duplication and foster regulatory trust. Moreover, leveraging real-world evidence, AI[120,121] and digital monitoring technologies[122] can improve decision-making while accommodating innovation. Continued investment in global regulatory alignment frameworks, particularly those focused on pandemic preparedness, will be key to ensuring timely, equitable access to next-generation mRNA vaccines[96].

Engineering strategies to increase accessibility

Addressing challenges in stability and delivery might enable broader global access to mRNA vaccines[123], for example, by improving thermostability, through alternative delivery strategies and carriers, by engineering RNA platforms (self-amplifying mRNA and circular mRNA), and using AI and machine learning approaches (Fig. 2). By changing how mRNA vaccines are stored and delivered, dose requirements can be lowered, administration simplified and distribution streamlined for vaccination in resource-limited settings.

Improving thermostability

Currently FDA-approved SARS-CoV-2 mRNA vaccines remain stable only for several days (mRNA-1273 for 30 days and BNT162b2 for 5 days) at 2–8 °C and require long-term storage at −20 °C or −70 °C, creating substantial cold-chain barriers[124]. To overcome the cold-chain dependence of mRNA–LNP vaccines, formulation and processing strategies have been developed to increase thermostability[125], including lyophilization with cryoprotectants, lipid-composition modification, addition of stabilizing excipients (encapsulation within protective matrices) and spray drying (Fig. 2a).

Lyophilization. Lyophilization (freeze-drying) can increase mRNA–LNP-vaccine stability by removing water in the presence of stabilizing excipients, converting formulations into dry powders with markedly increased shelf life at 4 °C or ambient temperature[126]. Cryoprotectant sugars, such as sucrose and trehalose, preserve nanoparticle structure and prevent mRNA degradation, allowing reconstituted vaccines to retain particle size, potency and immunogenicity[10,127–129]. Molecular dynamics simulations have further clarified how excipients and lipid components interact during drying and rehydration, guiding optimization of long-term stability[130]. For example, a lyophilized COVID-19 mRNA–LNP vaccine can maintain its physicochemical properties and immunogenicity for 6 months at 25 °C, eliciting robust neutralizing antibody responses without considerable adverse effects in mice, rabbits and macaques[131]. Similarly, the lyophilized mRNA–LNP vaccine CPVax-CoV, incorporating thiolactone-based ionizable lipids and UTRs designed to enhance expression, preserves full biological activity for up to 1 year at both 4 °C and 25 °C, and confers protection against SARS-CoV-2, including the Omicron XBB variant, in a mouse model[132].

Lipid design modification. Lipid components can be engineered to enhance the thermostability of mRNA–LNP vaccines. Modifying the chemical structure of lipids within LNPs improves mRNA stability during storage while preserving its functional activity after administration[10]. For example, aldehyde impurities that react with mRNA nucleosides can be reduced by chemically engineering ionizable lipids[133]. In particular, piperidine-based ionizable lipids limit aldehyde formation, preventing the formation of mRNA–lipid adducts, preserving mRNA activity and extending shelf life of mRNA–LNP formulations at 4 °C (ref. 133). Moreover, the imidazole-headed ionizable lipid DOG-IM4, which contains dioleoyl tails and a short polyoxyethylene spacer, substantially improves LNP stability, with >80% delivery activity retained after 25 weeks in liquid storage at 4 °C. Formulated with influenza haemagglutinin mRNA, DOG-IM4-based LNPs elicit robust immune responses in mice and non-human primates, including high haemagglutination-inhibiting antibody titres and T helper cell 1-skewed T cell responses[134].

Addition of stabilizing excipients. Thermostable mRNA–LNP vaccines can also be engineered by mixing them with or adding excipients, such as polymers, sugars or other stabilizing agents[135], to provide a protective matrix that prevents the degradation of mRNA–LNPs, improves stability under varying storage conditions and extends shelf life without requiring lyophilization. For example, embedding mRNA–LNPs in a polymeric film, composed of hydroxypropyl methyl cellulose, glycerol, surfactants and PEGylated lipid, preserves in vitro transfection efficiency for over 16 weeks at 4 °C (ref. 136). Additionally, dissolvable microneedle patches, made from a polyvinyl alcohol and polyvinylpyrrolidone blend, can be loaded with mRNA–LNPs and maintain stability for at least 6 months at room temperature[86].

Spray drying. Spray-drying techniques can be applied to produce inhalable dry powders of mRNA–LNPs that remain stable at ambient temperatures. These powders are reconstituted or administered

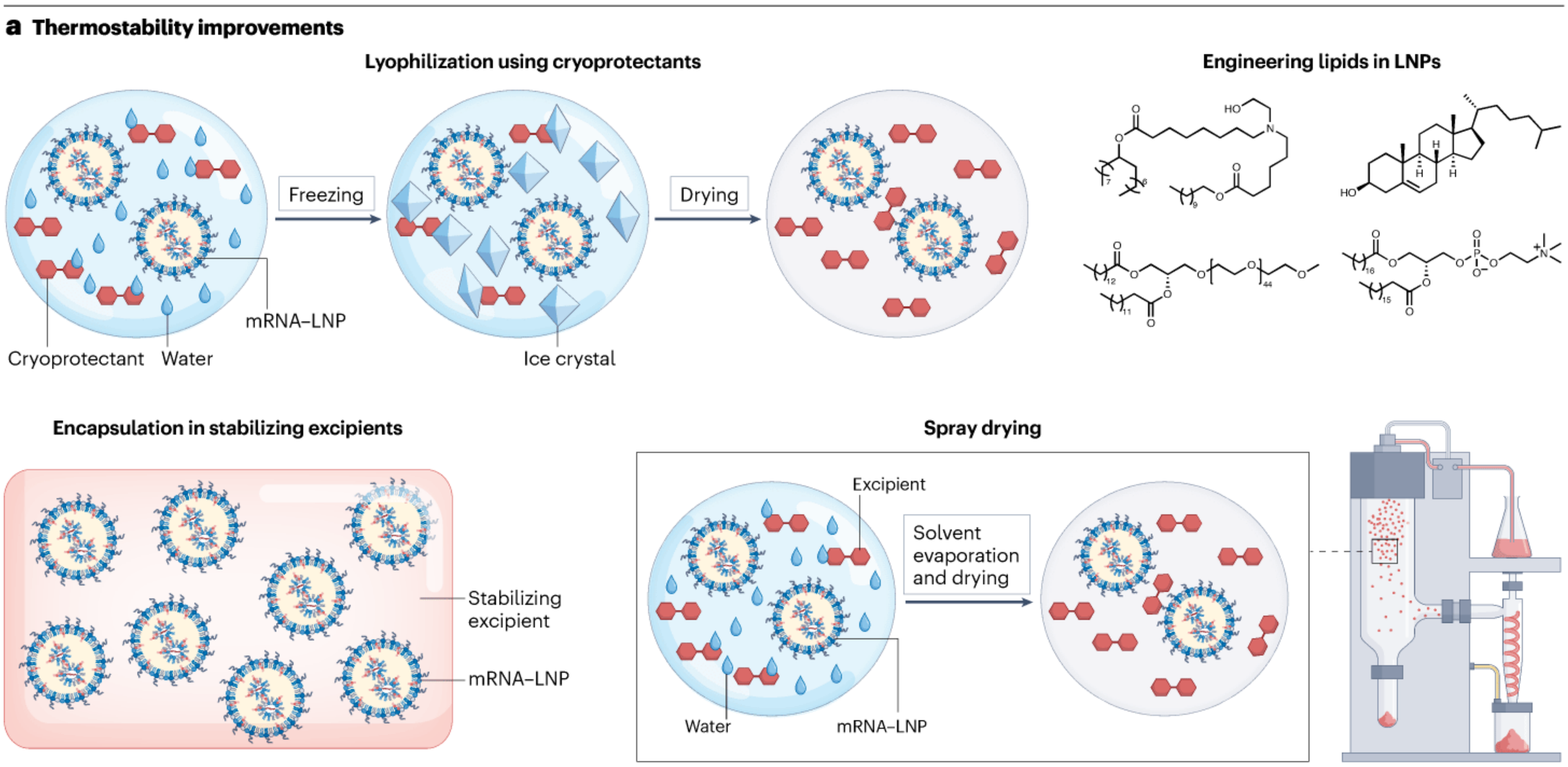


Fig. 2 | Engineering strategies to increase the accessibility of mRNA vaccines. a, Thermostability can be improved through lyophilization using cryoprotectants, by engineering lipids in lipid nanoparticles (LNPs), through encapsulation in stabilizing matrices and by spray-drying techniques. **b**, Alternative delivery approaches include diverse administration routes, such as intradermal delivery using microneedle patches, intradermal injection and mucosal delivery through intranasal or oral routes; delivery vehicles, such as polymeric nanoparticles, hybrid polymer–lipid nanoparticles, dendrimers and peptide-based nanoparticles; and hydrogel-based depot systems for sustained release. Alternative mRNA vaccine platforms include self-amplifying RNA and circular RNA. **c**, Artificial intelligence and machine learning strategies aim at enhancing mRNA stability and immunogenicity, optimizing LNP design and formulation, and optimizing manufacturing for scalability and efficiency.

directly through pulmonary routes, enabling cold-chain-independent deployment. For example, a spray-dried mRNA–LNP formulation, using a trehalose and trileucine mixture, retains mRNA integrity and functional protein expression in lung tissue following intratracheal delivery in rats[137]. Similarly, mannitol and leucine can be used to create an ethanol-based spray-dried mRNA–LNP powder, which shows improved dispersibility and statistically significantly enhanced in vivo lung transfection in a mouse model, compared with leucine alone[138].

Alternative delivery approaches

Alternative delivery methods, such as different administration routes; non-LNP nanocarriers; and alternative mRNA platforms, such as saRNA and circular RNA (circRNA), are being explored to increase mRNA vaccine accessibility, improve patient compliance and broaden immunization coverage (Fig. 2b).

Administration routes. Intramuscular injection remains an effective and commonly implemented route for mRNA vaccination. In addition, intradermal and mucosal administration are being explored for mRNA–LNP vaccines. Intradermal delivery takes advantage of the dense antigen-presenting cell network of the skin for dose sparing and reduced systemic reactogenicity, and microneedle patches enable pain-free, self-administered dosing, limiting sharp waste and healthcare provider burden, and stabilizing mRNA–LNPs in solid matrices for simplified storage and shipping. Mucosal routes (intranasal and oral) provide needle-free immunization at inductive sites, eliciting both local and systemic responses.

Intradermal delivery leverages the high density of antigen-presenting cells in the dermis to achieve immune activation with lower mRNA doses and fewer systemic side effects than intramuscular administration[139]. Clinical studies show that fractional intradermal doses of mRNA vaccines can elicit robust immunity[140,141]. In a proof-of-concept trial, one-fifth of the mRNA-1273 COVID-19 vaccine dose (10–20 μg versus 100 μg intramuscularly) given intradermally induced anti-spike antibody responses in all participants, with the 10 μg and 20 μg doses well tolerated and causing only mild local reactions[139]. These findings highlight the dose-sparing potential of intradermal delivery to extend vaccine supply, lower per-patient costs and improve accessibility. Additionally, needle-free intradermal jet injection (for example, PharmaJet Tropis) has been clinically deployed for mRNA platforms, including an saRNA COVID-19 booster delivered intradermally using Tropis, showing favourable safety and immunogenicity[25]. Laser-assisted intradermal delivery (fractional laser ablation) transiently disrupts the stratum corneum by creating microthermal channels that enhance penetration and antigen uptake in cutaneous antigen-presenting cells. This approach allows efficient needle-free mRNA delivery in preclinical models[142]. Intradermal delivery could be standardized using microneedle array patches[143]. For example, in rodent models, microneedle array patches can deliver mRNA–LNPs into the skin and elicit immune responses comparable with those achieved with intramuscular injection[86,87]. These COVID-19 mRNA–LNP patches remain stable at room temperature for at least 6 months and maintain functional efficacy in vivo[86]. Beyond improved stability, microneedle patches are simple to administer, reduce sharp waste and eliminate cold-chain requirements.

Mucosal routes, such as intranasal and oral administration, can induce local mucosal immunity and simplify vaccine logistics[144,145]. Intranasal delivery can protect the respiratory mucosa at the primary infection site, but it faces barriers from mucus and enzymatic degradation[146]. To overcome such barriers, nanoparticle formulations can be engineered to enhance mucosal absorption and protect mRNA, including mucoadhesive[147] and PEGylated LNPs with optimized PEG content for intranasal delivery[148]. Alternatively, dry powder aerosols can be produced by spray drying or spray freeze drying to generate respirable mRNA–LNP powders that maintain mRNA integrity, show improved stability at ambient temperatures and can be delivered using portable inhalers[137,149].

Oral mRNA vaccines face substantial gastrointestinal barriers, including acidic pH and digestive enzymes, that rapidly degrade unprotected nucleic acids[145]. To overcome these challenges, self-amplifying mRNA–LNPs can be designed with or without *Lactobacillus plantarum* to induce robust systemic IgG and mucosal IgA responses in mice, following oral delivery. This strategy results in T helper cell 1-skewed immunity and neutralizing activity against SARS-CoV-2 variants[150]. Similarly, IL-22 mRNA, delivered orally in ginger-derived nanoparticles, achieves localized protein expression in inflamed intestinal tissue and promotes resolution of colitis in mice[151]. A pH-responsive β-glucan-complexed mRNA–LNP system similarly protects mRNA in the gastrointestinal tract and elicits antigen-specific immune responses with enhanced antitumour efficacy in mice[152]. In addition, SARS-CoV-2 mRNA–LNPs, formulated as a mucoadhesive buccal film, composed of a pullulan–trehalose–sucrose matrix plasticized with glycerol on an ethyl cellulose backing, induces systemic immunity comparable with intramuscular injection and generates mucosal IgA in mice, highlighting the potential of needle-free booster strategies[153].

Alternative delivery carriers. Although LNPs have enabled the clinical success of mRNA vaccines, key areas remain under optimization, including durable antigen expression (limited by transient delivery and endosomal escape), tissue selectivity beyond the liver and dose-limited reactogenicity, motivating exploration of alternative or hybrid carriers, including non-LNP platforms and injectable or in situ-forming hydrogel depots[154–156]. These strategies can improve vaccine stability and enhance uptake; they also offer tuneable chemistry for ligand-directed tissue targeting and mechanics that enable controlled cargo release, concentrate mRNA at desired sites (for example, lymphoid or mucosal tissues), and support single-injection or extended-interval dosing through depot effects.

Biodegradable polymeric nanoparticles, such as FDA-approved poly(lactic-co-glycolic acid) (PLGA), offer stability and biodegradability, but interact weakly with negatively charged mRNA. However, co-formulation with cationic polymers, such as polyethyleneimine or poly-β-amino esters (PBAEs), enables mRNA encapsulation and cellular uptake[157,158]. PBAE-based nanoparticles allow oral mRNA vaccine delivery, inducing robust systemic and mucosal immune responses in vivo[159]. Polymer-based mRNA nanoparticles are typically more amenable to lyophilization than LNPs, supporting thermostability. Such nanoparticles have been applied in intranasal vaccines against respiratory infections[160]. Other cationic polymers, including chitosan and poly-L-lysine, similarly form polyplexes that facilitate mRNA delivery[161]. Notably, biodegradable poly(amine-*co*-ester) polyplexes enable inhalable mRNA vaccination, eliciting local and systemic immune responses in the lung and conferring protection against SARS-CoV-2 in mice[162]. Hybrid polymer–lipid nanoparticles further combine polymer core stability and controlled release with lipid-mediated uptake and endosomal escape, achieving high encapsulation efficiency and potent immune responses[163–165].

Dendrimer nanoparticles, with their highly branched architecture, also enable efficient mRNA delivery[166]. For example, ionizable

amphiphilic Janus dendrimers allow targeted mRNA delivery to murine lung parenchyma, demonstrating efficient and localized protein expression following intratracheal administration[167]. Similarly, a dendrimer–RNA nanoparticle vaccine generates both $CD8^+$ T cell responses and antibody responses against Ebola virus, influenza viruses and *Toxoplasma gondii* with a single dose[168]. Additionally, peptide-based nanoparticles, such as arginine-rich peptide-based mRNA nanocomplexes, induce cytotoxic T cell immunity in a mouse model, with the effectiveness dependent on the amphipathic organization of the peptide[169]. Moreover, the cell-penetrating peptide PepFect 14 can deliver mRNA into ovarian cancer cells, leading to transient protein expression both in vitro and in vivo, with expression localized to the peritoneal cavity[170].

Biodegradable hydrogels can be loaded with mRNA-encapsulating nanoparticles to allow controlled and sustained mRNA–nanoparticle release, extending antigen availability and potentially eliminating the need for multiple boosters[171]. Localizing mRNA at the injection site increases exposure to recruited immune cells, while limiting systemic distribution and off-target effects. In particular, single-dose hydrogel formulations could simplify vaccination schedules, reduce costs, improve compliance and enhance global mRNA vaccine accessibility. For example, an injectable polymer–nanoparticle hydrogel, comprising hydrophobically modified hydroxypropyl-methylcellulose (HPMC-C12) and poly(ethylene glycol)-*block*-poly(lactic acid) (PEG-*b*-PLA) nanoparticles, forms a shear-thinning, self-healing network. This hydrogel can be formulated with SARS-CoV-2 vaccine components and potent adjuvants, such as cytosine–phosphate–guanine (CpG) oligodeoxynucleotide or alum, to create a subcutaneous depot that persists for ~2–4 weeks, enabling sustained co-release of mRNA–nanoparticles and adjuvant, achieving rapid and durable antibody responses from a single dose in mice[172].

In addition, an mRNA–LNP-incorporated nanofibre–hydrogel composite can recruit immune cells and sustain local antigen expression, with a single subcutaneous dose eliciting antigen-specific T cell and antibody responses, comparable with a three-dose LNP regimen, improving tumour control in mice[156]. An injectable polymer–nanoparticle hydrogel, made of HPMC-C12 and PEG–PLA nanoparticles to depot mRNA–LNP vaccines, can create a local 'immune niche' that recruits antigen-presenting cells. This system can deliver a commercially available SARS-CoV-2 mRNA vaccine from this depot, thereby improving germinal centre durability and increasing the magnitude, breadth and durability of antibody responses[154]. Similarly, a thermoresponsive PLGA–PEG–PLGA gel, embedding PBAE mRNA nanoparticles encoding a signal 2 co-stimulatory molecule (4-1BBL) and a signal 3 immuno-stimulatory cytokine (IL-12), reprograms tumour cells towards antigen-presenting phenotypes, after a single intratumoural dose in mice[155]. In combination with anti–PD-1 immune checkpoint blockade, the PBAE nanoparticle formulation (4-1BBL/IL-12/CpG) reduces E0771 tumour burden, prolongs survival and protects against distant re-challenge[155].

Alternative mRNA vaccine platforms. Linear mRNA vaccines face challenges of stability, expression and reliance on cold-chain logistics. Alternatively, saRNA[173] and circRNA[174] have the potential to improve antigen-expression durability (through intracellular amplification for saRNA and increased nuclease resistance for circRNA) and reduce dose requirements[12], potentially promoting vaccine accessibility in resource-limited settings[175].

saRNA incorporates replicase genes that enable intracellular RNA amplification, yielding more antigen per dose than non-replicating linear mRNA[27,173]. saRNA technology has progressed from preclinical development to first-in-human clinical evaluation over the past 5 years[176]. Although recombination between saRNA vaccines and circulating alphaviruses is a theoretical concern, multiple factors mitigate this risk: expression of saRNA replicase can induce superinfection exclusion, limiting secondary alphavirus infection, but does not completely prevent co-infection; stringent co-infection and sequence-homology requirements make productive recombination unlikely; structural genes can be deleted in saRNA constructs to limit the emergence of replication-competent chimaeras; rare in vitro recombinants show poor fitness; and recombinant virus has not yet been detected in vivo[177]. Clinical trials, particularly for COVID-19 vaccines, have shown that saRNA vaccines are safe, immunogenic and effective at low doses[176,178]. Preclinical studies in animal models against viruses such as Ebola virus, RSV and influenza viruses have demonstrated potent protective immunity[179–181]. In oncology, saRNA vaccines can stimulate tumour-specific T cell responses and synergize with immunotherapies[182]. In addition, saRNA constructs encoding cytokines, such as IL-2, can eradicate established tumours and enhance T cell infiltration in melanoma models[183]. Formulation of saRNA vaccines with nanostructured lipid carriers endows them with thermostability. Such formulations can maintain efficacy for at least 6 months at room temperature and for at least 10 months at refrigerated temperatures[175]. However, saRNA replication produces dsRNA intermediates that strongly activate innate immune pathways. Although such adjuvant-like signalling can benefit vaccines, it may limit suitability for applications requiring minimal innate immune activation.

Engineered circRNAs are covalently closed, exonuclease-resistant transcripts that enable prolonged and enhanced protein expression without requiring chemical modification[174]. Across oncology and infectious disease models, circRNA vaccines encoding tumour or viral antigens can generate robust and durable immune responses, including against cancer[184], SARS-CoV-2 variants[185] and Zika virus[186], demonstrating the broad applicability of this platform. Moreover, cap structures and internal translation elements can be engineered to provide additional translation control and further boost protein output beyond the gains afforded by circular topology alone[187–189]. LNP-encapsulated circRNA can retain antigen expression after 2 weeks at 25 °C, and it shows minimal loss of activity after 28 days at 4 °C, outperforming modified and unmodified linear mRNA across all tested temperatures in an in vitro preclinical SARS-CoV-2 model[190]. These LNP-formulated circRNA vaccines can also produce more durable antigen expression and stronger T helper cell 1-skewed immunity than 1-methyl-pseudouridine-modified linear mRNA, eliciting high neutralizing antibody and T cell responses, and conferring protection in both mice and rhesus macaques[190]. An LNP-encapsulated circRNA vaccine encoding tumour antigens produces durable antigen expression, robust antitumour immunity and improved therapeutic efficacy, demonstrating its potential for cancer immunotherapy in a mouse model[191,192]. However, circRNAs require substantial engineering for robust cap-independent translation and pose challenges with regard to incomplete circularization and purity (for example, residual linear or dsRNA species), with limited clinical experience thus far.

Artificial intelligence and machine learning strategies

AI and machine learning approaches can be applied to improve the thermal stability and efficacy of mRNA–LNP vaccines, and to expedite their development and deployment[193], making vaccines more accessible[72,194] (Fig. 2c). In particular, AI and machine learning can optimize the stabilization of mRNA molecules, aid in the design of lipid carriers and

production methods, and accelerate vaccine target discovery[195]. For example, reverse vaccinology can be combined with machine learning to predict B cell and T cell epitopes and prioritize SARS-CoV-2 antigens capable of eliciting robust immune responses[196].

mRNA stability and immunogenicity. AI and machine learning can be applied to design stable mRNA sequences[72]. For example, a crowd-sourced machine learning competition resulted in models that predict RNA backbone hydrolysis with high single-nucleotide accuracy, which can be generalized to full-length mRNAs, providing a foundation for designing mRNA transcripts with improved shelf life[197]. In addition, the LinearDesign algorithm applies a dynamic programming approach to simultaneously optimize secondary structure stability and codon usage of mRNA. In tests on SARS-CoV-2 and other vaccine antigens, LinearDesign could substantially extend the mRNA half-life and protein expression, leading to up to 128-fold higher antibody titres in mice compared with a codon-optimized mRNA sequence[194]. Moreover, deep learning can predict mRNA structure and stability, guiding the rational optimization of 5′UTRs to improve mRNA stability and translational efficiency[73].

LNP design and formulation optimization. Machine learning methods can also be leveraged to optimize LNP formulations that protect and deliver mRNA[198,199]. For example, a machine learning model (LightGBM) trained on 325 mRNA–LNP formulations accurately predicted vaccine-induced antibody titres ($R^2 > 0.87$)[200]. AI can be further integrated with high-throughput screening to rationally design new lipids. For example, nearly 20 million virtual lipid structures were evaluated by an AI-driven pipeline, yielding several new ionizable lipids that match or surpass the delivery efficiency of benchmark lipids, such as MC3 and SM-102, in mouse models[201]. Similarly, the AGILE (AI-guided ionizable lipid engineering) platform reduces lipid discovery timelines from months or years to days[202]. Furthermore, machine learning can be integrated with combinatorial chemistry to improve mRNA delivery efficiency, reducing experimental burden[203]. Beyond formulation optimization, predictive modelling, generative adversarial networks and neural networks enable RNA–LNP engineering for cancer vaccines, resulting in improved tumour targeting and more efficient formulation design[204]. AI can also accelerate the design and effectiveness of personalized cancer immunotherapies[205]. For example, machine learning and deep learning enable neoantigen discovery, codon and UTR optimization, and mRNA vaccine design, enhancing immunogenicity, protein expression and mRNA stability[205]. In neoantigen discovery, these models integrate peptide–major histocompatibility complex (MHC) binding, antigen processing and T cell receptor recognition to improve prediction of immunogenic targets[205,206] while addressing challenges such as data scarcity, tumour heterogeneity and model interpretability[205].

Process optimization for manufacturing and stability. Machine learning techniques can be applied to improve the manufacturing and formulation process of mRNA–LNP vaccines. For example, algorithms such as XGBoost can be combined with Bayesian optimization and self-validated ensemble to fine-tune microfluidic mixing conditions and lipid ratios during LNP production[207]. By training on a designed set of formulation experiments (for example, varying component ratios and flow conditions), these models accurately predict crucial quality attributes, such as particle size, polydispersity index, encapsulation efficiency and stability, achieving >97% prediction accuracy and particle sizes (~95–97 nm) closely matching those of experimental results[207]. Similarly, a combinatorial artificial neural network–design-of-experiment approach can predict and optimize mRNA–LNP vaccine formulations by evaluating lipid type, amine/phosphate ratio, flow rate ratio and total flow rate to control particle size, polydispersity index, zeta potential and encapsulation efficiency[208].

Local manufacturing and capacity building

The expression ‘resource-limited settings’ refers to regions or communities with constrained health systems and infrastructure[209,210]. Constraints vary across settings and may include limited healthcare infrastructure, cold-chain distribution, storage capacity, trained healthcare workers and supply chains[211]. For example, limited local production facilities can limit access to vaccines. In addition, the specialized equipment required for quality assessment of mRNA–LNPs, as well as its maintenance and calibration, may be scarce or difficult to sustain. Furthermore, deployment of mRNA vaccines might be negatively affected by the pace of technology transfer and limited regional manufacturing scale-up, as well as licensing and intellectual-property considerations[212,213]. Some of these barriers could be addressed by simplifying vaccine production, reducing costs and decentralizing manufacturing[214,215].

Localizing and scaling down manufacturing enable regional production to avoid reliance on imports from high-income regions[216]. For example, the modular ‘BioNTainer’ system is a plug-and-play mRNA manufacturing facility housed in shipping containers. In 2023, the first mRNA vaccine factory built from BioNTainer units was launched in Kigali, Rwanda, capable of end-to-end GMP production. Each modular unit (~800 m^2) can produce up to 50 million doses annually and includes independent power and climate control, reducing reliance on existing infrastructure. Planned expansions to Senegal and South Africa further illustrate how decentralized manufacturing could improve regional self-sufficiency and reduce dependence on cold-chain transport.

Similarly, the Ntensify mRNA platform was deployed at the Africa WHO mRNA Hub, supported by a US$40 million Gates Foundation initiative. Ntensify is a construct-agnostic mRNA-saRNA platform that integrates one-pot in vitro transcription with co-transcriptional capping, single-step purification, pre-mixed reagents and single-use disposables, enabling GMP production of ~1–5 g batches with a minimal footprint and without traditional scale-up transfer. In a related initiative, the Decentralized and Accelerated mRNA Vaccine Production System (DeCAFx), led by the International Vaccine Institute, seeks to deploy modular, regionally located mRNA-manufacturing units, aligned with the 100 Days Mission, integrating in vitro transcription, formulation and quality control in compact footprints to enable rapid vaccine responses and reduce dependence on centralized manufacturing hubs. BioNet-Asia established a GMP-compliant mRNA manufacturing platform in Thailand, supported by partnerships with Chulalongkorn University, the University of Pennsylvania and CEPI. The resulting ChulaCov19 vaccine advanced through phases I and II trials, demonstrating safety and immunogenicity, particularly as a heterologous booster, highlighting the potential of regionally developed mRNA vaccines tailored to local needs[217,218].

mRNA vaccine access might be further improved through capacity-building by technology transfer. For example, the WHO has led an mRNA Technology Transfer Programme to train and equip manufacturers in several LMICs to produce mRNA vaccines using a multilateral

technology-sharing model[219]. A WHO-supported South African mRNA vaccine was developed by the biotechnology company Afrigen and is based on the sequence of the VAC 2121 vaccine[220,221]. Additionally, Afrigen has trained 15 partners (Argentina, Bangladesh, Brazil, Egypt, India, Indonesia, Kenya, Nigeria, Pakistan, Senegal, Serbia, South Africa, Tunisia, Ukraine and Vietnam) to initiate and develop their own mRNA vaccines programmes, aiming to produce vaccines that are affordable and tailored to their storage realities[220].

Ethical and social considerations

Ethical and social considerations in the development and deployment of mRNA vaccines[222] include equitable distribution, community engagement and vaccine hesitancy.

Equitable distribution

Achieving equitable distribution of mRNA vaccines requires more than scaling up production; it necessitates addressing systemic barriers that limit global access[223]. By January 2023, over 13 billion doses of COVID-19 vaccine had been administered worldwide[218]. However, inequities persist, with only 25% of people in LMICs having received at least one dose, compared with more than 70% in high-income nations[218]. This disparity underscores the need for strategies that prioritize equitable vaccine distribution globally[109]. Public and multilateral investment has played a central role in accelerating mRNA vaccine development and access. In the USA, federal investment in mRNA COVID-19 vaccines totalled approximately US $31.9 billion (ref. 224), with ~US $337 million allocated before the COVID-19 pandemic. Prior to COVID-19, the National Institutes of Health (NIH) contributed US $116 million (35%) towards basic and translational mRNA vaccine research, whereas the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense invested US $148 million (44%) and US $72 million (21%), respectively[224]. During the COVID-19 pandemic, most public funding (US $29.2 billion; 92%) supported vaccine procurement, with US $2.2 billion (7%) directed to clinical trials and US $108 million (<1%) to manufacturing and foundational research[224]. These investments underscore the crucial role of government funding in accelerating innovation and ensuring public access. However, NIH support for mRNA and HIV vaccine research has undergone a phase-out of targeted initiatives (for example, the National Institute of Allergy and Infectious Diseases (NIAID) and the Center for HIV/AIDS Vaccine Development (CHAVD) HIV-vaccine consortia will not continue beyond the current cycle), and supplements established during the COVID-19 pandemic have concluded, underscoring the need for sustained, predictable private and other investment strategies to maintain momentum and avoid losing progress.

Globally, initiatives such as COVAX, co-led by Gavi, the Vaccine Alliance, the CEPI and the WHO, with UNICEF as a delivery partner, pooled resources to accelerate vaccine development, manufacturing and procurement[225]. Supported by governments, international agencies and philanthropic donors, COVAX delivered nearly two billion doses to 146 countries, with ~90% reaching LMICs.

Community engagement and vaccine hesitancy

Equitable distribution alone is insufficient without public acceptance, particularly during pandemics, when rapid uptake is essential[211,226]. Vaccine hesitancy arises from mistrust in institutions, misinformation, historical healthcare injustices and concerns over safety and rapid development, all of which contributed to COVID-19 vaccine reluctance[210,211]. Community engagement is therefore crucial for building trust and promoting clear, accessible communication about vaccine safety and efficacy[227].

The technology underlying mRNA vaccines has been in development for decades. mRNA was first discovered in 1961, and clinical trials of mRNA-based therapeutics began in the early 2000s[6,7]. Transparent communication about this long-standing scientific foundation can play an important role in building public trust and countering misinformation[228,229]. Healthcare providers are often regarded as the most trusted sources of information on vaccination; therefore, both scientists and healthcare professionals should engage in transparent communication to foster public confidence and sustain high vaccine uptake[117,118]. Training healthcare, faith and community leaders to communicate scientific information might further enable culturally tailored outreach and strengthen local advocacy.

Addressing misinformation is essential to reducing hesitancy[230]. For example, proactive engagement with digital platforms can aid in identifying and countering false vaccine-related content[231]. Initiatives such as the Vaccine Confidence Project[232] monitor public trust and misinformation globally, providing early-warning signals that inform targeted policy and communication strategies. Notably, populations in LMICs demonstrated higher willingness to receive COVID-19 vaccines than those in the USA (mean 64.6%) and Russia (mean 30.4%), driven by perceived risk, trust in health professionals and familiarity with vaccination campaigns[226,233]. These findings highlight the importance of context-specific engagement strategies to promote equitable vaccine uptake worldwide.

Outlook

Transforming mRNA vaccines from emergency solutions into routine, equitable tools requires overcoming three key access barriers: stability to reduce cold-chain requirements, durability to reduce dose and immunizations, and scalable delivery to allow low-cost and decentralized administration. For indications requiring durable immunity (for example, HIV), solid-state, slow-release mRNA vaccines could offer a solution. For example, SEAL (stamped assembly of polymer layers) microparticles can serve as solid-state depots that enable controlled release, prolonging antigen exposure and strengthening immune responses[234–236]. SEAL microparticles can be further embedded in hydrogel depots to provide a single localized reservoir[237]; building on this design, mRNA–LNPs could be incorporated into a hydrogel to enable rapid antigen release, whereas SEAL microparticles would provide a built-in delayed booster, with release kinetics tuneable through PLGA molecular weight and PLA:PGA monomer ratio. By reducing cold-chain dependence and enabling single-injection dosing, SEAL platforms could improve accessibility in high-burden settings. In addition, saRNA, circRNA, new hybrid nanocarriers and thermostable formulations aim to improve stability, potency and reach in resource-limited settings. Integrating AI and machine learning across antigen selection, sequence design and formulation optimization can enhance immunogenicity, shorten development cycles and ultimately improve accessibility.

Establishing regional manufacturing hubs is essential for decentralized production, equity and pandemic readiness. Delivering on this vision will require regulatory and reliance mechanism alignment, structured technology transfer, training, capacity-building, and sustained investment in regional manufacturing and quality systems. Moreover, public–private partnerships linking governments, academia and industry, supported by multilateral and philanthropic funders, play an important role in expanding capacity and lowering costs. Equitable vaccine uptake also requires sustained community engagement,

cultural sensitivity and inclusive research practices that empower local voices and foster trust in public health systems. If executed at scale, this agenda will make mRNA vaccine platforms more accessible and affordable, advancing equity in global health.

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Author contributions

Conceptualization: B.E. and A.J. Writing — original draft, figures and tables: B.E. Writing — review & editing: B.E., R.L. and A.J. All authors reviewed and approved the manuscript prior to submission.

Competing interests

From fiscal year 2021 to the present, R.L. has received licensing fees (to patents in which he was an inventor on) from, invested in, consulted (or was on Scientific Advisory Boards or Boards of Directors) for, lectured (and received a fee), or conducted sponsored research at the Massachusetts Institute of Technology for which he was not paid, for the entities listed in the Supplementary Information. From fiscal year 2021 to the present, A.J. has received licensing fees (to patents on which she was an inventor) from, invested in, consulted (or was on Scientific Advisory Boards or Boards of Directors) for, lectured (and received a fee), or conducted sponsored research at the Massachusetts Institute of Technology for which she was not paid, for the following entities: The Estée Lauder Companies, Moderna Therapeutics, OmniPulse Biosciences, Particles for Humanity, SiO2 Materials Science, VitaKey.

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